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TITLE: Neurobiology of Sleep and Sleep Treatments in PTSD (NOS-STIP)

PRINCIPAL INVESTIGATOR: Dr. Anne Germain

CONTRACTING ORGANIZATION: University of Pittsburgh
Pittsburgh, PA 15213

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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14. ABSTRACT

This is an annual progress report that covers the funding period included between 9/15/2010 to 3/17/2010. Recruitment is ongoing. Our recent successes with new recruitment strategies, expanding collaborative relationships with local and regional resources for veterans have yielded to a greater number of contacts from interested individuals and potential research participants. The randomized controlled trial is exclusively focused on recruiting OEF/OIF returnees. Reportable outcomes include research abstracts, and research training activities. Archival PET data analyses are under way and will better contextualize the anticipated findings from this proposal with veterans with and without PTSD.

15. SUBJECT TERMS

Sleep, PTSD, PET neuroimaging, prazosin, placebo, randomized controlled trial

Table of Contents

PT073961: *Neurobiology of Sleep and Sleep Treatments in PTSD (NOS-STIP)*

Annual Technical Progress Report
Progress Period: September 15 to September 8, 2010

I. INTRODUCTION

Posttraumatic stress disorder (PTSD) adversely affects daytime functioning and sleep. Sleep disturbances also independently contribute to poor clinical outcomes, and are often resistant to first-line PTSD interventions. Sleep-focused treatments are often required to alleviate nightmares and insomnia in PTSD patients. These observations suggest that the neurobiology of sleep is altered in PTSD, and that first-line PTSD treatments fail to normalize PTSD-related neurobiological changes during sleep. Our study aims at comparing the neurobiological correlates of REM sleep and NREM sleep relative to wakefulness in OIF/OEF returnees with and without PTSD by using state-of-the science sleep neuroimaging [^{18}F]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET). Returnees with PTSD then complete in an 8-week, double-blind, placebo-controlled prazosin trial, and repeat sleep and PET studies post-treatment. This will allow for investigating 1) pre-treatment neurobiological sleep predictors of sleep treatment response, and for evaluation pre- to post-treatment changes in neurobiological correlates of REM sleep and NREM sleep associated with sleep treatment response.

This progress report covers the performance period included between September 15 2009 and September 8, 2010. Progress specific to the last three-month period of performance is also included and described when relevant.

II. BODY

Research accomplishments associated with each task outlined in the approved Statement of Work. The tasks and timeline initially proposed and approved in the approved Statement of Work are provided below. Progress and outcomes on each of the task listed are detailed for this review period.

Task 1: Recruit, screen, and randomize 40 adult male and female military veterans with Posttraumatic Stress Disorder (PTSD) and 20 OIF/ OEF returnees without PTSD from ongoing and additional public advertisement and from the VAPHS (Months 6 – 45; NCTRC).

- ***Obtain and renew human subject research approvals (Month 1-6; NCTRC):***

Progress: This sub-task has been completed. The University of Pittsburgh IRB reviewed and approved continuation of this proposal in June 2010. A protocol to include the clinical trial previously conducted under a separate award was submitted to the University IRB, as requested by the University IRB, because the initial proposal only covered the additional sleep and neuroimaging studies required by the current award, whereas the clinical trial was conducted under a separate protocol. The new protocol and related consent forms now act as stand-alone documents, independent from the previous clinical trial, and were approved on 7/9/2010 (University of Pittsburgh IRB approval letter provided in Appendix)

- ***Hire and train research assistant who will be in charge of recruitment, MR, and PET scheduling (Month 1-6; NCTRC)***

Progress: In the last period of performance, we have hired two new staff member, Rachel Good (research assistant) and Jessica Boarts, PhD (coordinator) to replace Ms. Julia Chasler and Mr. Ryan Stocker, who both left their position on staff to pursue graduate studies in clinical psychology and clinical counseling, respectively. Mr. Stocker remains on staff at 10 hours per week while the training and transition period with Dr. Boarts is being finalized. It is expected that Mr. Stocker will terminate his contribution to our team in October 2010.

Support for PET data management was redistributed to Ms. Mary Fletcher (previously to Mrs. Annette Wood) and support has been lowered to 2.5% to reflect the lower data load generated by the study in the previous performance period.

- ***Develop advertisement material and disseminate information about this new sleep neuroimaging research arm and referral process to clinical staff of the VA Pittsburgh PTSD programs and local units (Months 6-42; NCTRC)***

PROGRESS: We continue to work with local media and to gather feedback from research participants to refine and improve our recruitment materials. Continuing outreach efforts include collaborations with the University of Pittsburgh Veterans' Office, and the Pittsburgh Veterans Leadership Program. In addition, we have had the opportunity to provide an internship site for the University of Pittsburgh Reserve Officers' Training Corps [ROTC] program, and have recruited and trained Mr. Benjamin Paul (senior student at the University of Pittsburgh ROTC program, majoring in Psychology with related field in political sciences) on our team. His role is to conduct outreach activities with local military units and resources and to distribute informational and recruitment pamphlets and flyers to interested leaders and individual military personnel.

Importantly, the University of Pittsburgh PET center closed its operations in July and August, for the replacement of our cyclotron. Because of this closure, we had to slow down recruitment efforts during this period, since PET studies were not available. We also refrained from recruiting participants so that we would not have to withhold participation for over 2 months, and delay treatment entry for veterans with clinically significant sleep disturbances and PTSD. The UPMC PET center has now re-opened its operations for sleep neuroimaging studies, and is now providing additional time slots and coverage to compensate for the lost time incurred over the past summer.

We have thus further intensified recruitment, through local newspaper, radio, and television advertisements. We have also distributing flyers to households with veterans, as determined by the local *Tribune* newspaper. This process is entirely handled by the contractor, so that we do not have access to identifiable information, unless interested veterans who may receive flyers contact us directly and express interest in the study.

- ***Recruit and conduct diagnostic, physical, and sleep disorders screenings in eligible participants (Months 6-42; NCTRC)***

PROGRESS: The recruitment flowchart to date is provided in the recruitment flow chart, and is included in the Appendix. Since the beginning of the study, we have been contacted by a total of 375 individuals through a variety of recruitment sources. Of these, 215 were contacted and received at least some information about the study at the initial telephone contact (scripted). During the telephone screen, 138 provided exclusionary information and were found ineligible for the study, and 46 completed the telephone screening questions to assess eligibility. Fifty-four individuals declined the telephone screening because of 1) recall to active duty; 2) participation burden; 3) no longer interested in a research study; 4) unable to accommodate the requirements for travel or

time commitment. Of the 46 individuals who completed the telephone screening, 39 were found to be eligible and were invited for a consent visit. Fifteen were excluded prior to consent due to no-shows and were no longer interested or able to participate in the study. Eight were excluded after providing written, informed consent due to 1) positive drug screen; 2) AHI > 15; 3) were found to have a diagnosis of bipolar disorder or active substance abuse; 4) or were unable to continue participation. A total of 18 OEF/OIF veterans were consented to date: 10 non-PTSD ("control" in flowchart) and 8 with PTSD. Of the 10 non-PTSD subjects, 5 have completed the protocol, and 2 are currently actively enrolled in the study. Three were excluded because of poor compliance with study procedures (n = 2), and 1 was found to have a positive drug screen on the first sleep night in the laboratory. Of the 8 subjects with PTSD, three are currently active in the screening of baseline phase of the study, and five have been excluded during the screening phase for poor compliance (n =2), and active bipolar disorder (n = 1). Two more PTSD participants have been consented after the recruitment flowchart was produced and are ongoing screening procedures.

- ***Randomize eligible participants with PTSD into the ongoing treatment trial (Months 6-42; NCTRC). For participants randomized to the medication arms (prazosin or placebo), complete screening magnetic resonance (MR) scans. (Months 6-42; UPMC MR Center)***

PROGRESS: This sub-task is ongoing. We have 3 participants with PTSD who are completing the screening or baseline phase of the study, who will then be randomized to the treatment phase. Two more PTSD participants have been consented after the recruitment flowchart was produced and are ongoing screening procedures. All eligible non-PTSD participants completed the study procedures as planned.

Recruitment of OEF/OIF veterans continues to be challenging and appears to be a general challenge encountered by our colleagues at other institutions, as well as clinicians working in behavioral health care clinics. We have been able to consent 18 of 39 individuals invited for a consent visit (46%), but the rate of enrollment relative to the number of individuals reached and interested in the protocol ("scripted") is 8.4% (18 of 215 individuals) is lower. This enrollment rate is nevertheless consistent with our prior experience and literature on clinical trials on treatments of sleep or PTSD studies.

After consulting with Dr Kimberly Del Carmen and Dr. Murray Raskind in June 2010, we are in the process of making the necessary modifications to the protocol to open recruitment to military veterans with PTSD who are currently using one SSRI.

However, we are also considering alternative options, including expanding recruitment to veterans of other conflicts (but within the same age range), or to civilians with PTSD. We will, of course, seek advice from the program officials shortly to identify the best strategy to accelerate recruitment and assure success of this study prior to implementation.

Task 2: To compare the neurobiology of PTSD during REM sleep and NREM sleep relative to wakefulness in returnees with and without PTSD (Months 6-48; NCTRC and UPMC PET Center).

- ***Conduct pre-treatment (baseline) clinical, polysomnographic, and PET scan studies in participants with PTSD who elect to take part in this study (Months 6-42; NCTRC, UPMC PET Center).***
- ***Recruit age- and sex-matched returnees without PTSD (Months 9-45; NCTRC)***

PROGRESS: This sub-task is ongoing. A total of 10 participants without PTSD (all men; age range 23 to 32) have been consented, and five have completed the study procedures.

- ***Process MR and PET scans (Months 6-46; NCTRC and PET)***

PROGRESS: This sub-task is ongoing. Imaging data review, alignment, processing, and archiving for analysis is conducted on a timely manner.

- ***Conduct preliminary and confirmatory statistical analyses with Statistical Parametric Mapping, version 2 (SPM-2) to evaluate Group (PTSD vs. Non-PTSD) X State (Wakefulness vs. NREM; Wakefulness vs. REM sleep) differences in absolute and relative regional cerebral metabolic rate of glucose (rCMRglc; Months 36-48; NCTRC).***

PROGRESS: This sub-task is not applicable for this review period. However, the PI has completed a lecture series on the most recent version of SPM (SPM8) for PET data analyses, and this most recent version will be used for data analysis. Preliminary analysis using data collected from veterans who completed the study to date will be initiated shortly. Specifically, we plan to compare brain glucose metabolism during REM and NREM sleep relative to wakefulness in OEF/OIF veterans enrolled to date, to brain activation patterns in these sleep stages relative to wakefulness observed in sex and age-matched civilian healthy sleepers, and civilian patients with depression. These contrasts will allow characterizing how brain activity across the sleep-wake cycle may be affected by combat exposure in a preliminary manner.

- ***Conduct preliminary and confirmatory statistical analyses with SPM-2 to evaluate the neurobiological correlates of nightmares and insomnia during REM and NREM sleep in PTSD patients (Months 36-48).***

PROGRESS: This sub-task is not applicable for this review period.

Task 3: To identify the neurobiological changes associated with sleep treatment response during REM sleep and NREM sleep relative to wakefulness.

- ***Administer and monitor treatment protocols in participants with PTSD (Months 6-45; NCTRC)***

PROGRESS: As indicated above, sub-tasks related to recruitment, randomization, and treatment have been hampered earlier. Treatment protocols with prazosin and placebo are maintained as originally proposed. We do not anticipate problems in administering and monitoring treatments in participants with PTSD who will initiate treatment in the coming funding period. We now have consented 8 participants with PTSD, and three are expected to initiate the treatment phase in the coming weeks.

- ***Conduct and complete 8-weekly treatment sessions and weekly ratings of clinical changes, treatment adherence, and side effects (Months 6-45; NCTRC)***

PROGRESS: Treatment protocols with prazosin and placebo are maintained as originally proposed. We do not anticipate problems in administering and monitoring treatments in participants with PTSD who will initiate treatment in the coming funding period. We now have consented 8 participants with PTSD, and all are expected to initiate the treatment phase in the coming weeks.

- ***Monitor safety and adverse events (Months 6-45; NCTRC)***

PROGRESS: Protocols for monitoring and reporting safety and adverse events have been established, and are reviewed monthly with the study physician and investigators.

- ***Complete post-treatment assessments by using polysomnographic studies and PET scan studies, clinician-administered and self-report scales of sleep quality and disturbances, PTSD symptom severity, depression, anxiety, and health-related quality of life in participants with PTSD who complete the treatment protocol(Months 9-45; NCTRC)***

PROGRESS: Protocols to complete post-treatment assessments and procedures are in place.

- ***Identify treatment responders and non-responders. sleep treatment response is defined as a post-treatment sleep latency < 30 minutes, and wake time after sleep onset < 30 minutes, and a sleep efficiency > 85% as determined by sleep diaries and in-home sleep studies, or a decrease in > 5 points on the Pittsburgh Sleep Quality Index; and a decrease of 50% nightmares frequency as assessed by prospective logs.***
- ***Initiate and complete preliminary and confirmatory data analyses to assess pre- to post-treatment changes in rCMRglc from wakefulness to REM sleep and to NREM sleep in treatment responders vs. non-responders (to prazosin, BSI, or placebo), and post-treatment changes in rCMRglc in responders and non-responders to rCMRglc data acquired in healthy subjects.***

PROGRESS: These sub-tasks are not applicable for this review period.

Task 4: To identify the neurobiological predictors of sleep treatment response (Months 9-48; NCTRC)

- ***Initiate and complete preliminary and confirmatory data analysis to assess baseline differences in absolute and relative rCMRglc during wakefulness, REM sleep, and NREM sleep in treatment responders and non-responders with SPM-2 (Months 36-48; NCTRC).***

PROGRESS: Data necessary to initiate this sub-task are not yet available. We have nevertheless initiated preliminary analysis using data collected in a small sample of in adult civilians with primary insomnia as part of another study, to explore the regions of interest most likely to change in response to the treatment of insomnia.

Task 5. Prepare and submit research reports (NCTRC) (Months 32-48; NCTRC).

PROGRESS: This sub-task is not applicable for this review period.

III. KEY RESEARCH ACCOMPLISHMENTS

None to report at this time.

IV. REPORTABLE OUTCOMES

Research training activities conducted under this award in the past year.

Undergraduate training:

1. Mr. Benjamin Paul is a Psychology major student at University of Pittsburgh and is enrolled in the Army ROTC program completed a summer internship in clinical research with us. He was actively involved in outreach and recruitment efforts to augment

recruitment for the study. He has also completed a review of the literature on the comorbidity and characteristics of PTSD and mild traumatic brain injury.

2. Mrs. Olga Milgrom is a 1st year medical student at the University of Pittsburgh School Medicine, completed her summer research internship on August 9th. She completed PET data analysis training, and conducted preliminary analysis to identify neurobiological correlates of treatment response to a sleep-focused cognitive-behavioral treatment by conducting archival data analysis. The results of this preliminary study suggest that treatment of insomnia is associated with greater reductions in thalamic and associative cortical regions from wakefulness to NREM sleep post-treatment relative to pre-treatment. This preliminary study provides some insights into the potential subcortical and cortical neural correlates of sleep treatment response to contrast with the anticipated results of the present study using prazosin and placebo. These preliminary findings also provide initial information regarding the potential neural correlates of sleep treatment response in general, relative to the neural correlates of sleep treatment response to prazosin. Findings from this preliminary study will be submitted for the SLEEP 2011 Annual meeting as a research abstract for an oral presentation. A working draft of the abstract summarizing her work is provided in the appendix.

3. Mrs. Tanisha Hill-Jarrett is a Psychology Honors Student at University of Pittsburgh completed her work on the neurobiological correlates of NREM sleep relative to wakefulness in adults with depression compared to participants with primary insomnia. She successfully defended her honors dissertation defense on April 5, 2010. This project directly relates to the present study in identifying the potential neurobiological differences that characterize major depression and insomnia, two frequently comorbid conditions in military veterans with PTSD. Preliminary findings suggest that brain areas and structures involved in sleep and arousal regulation show different activation and deactivation patterns in these two clinical groups from wakefulness to non-REM sleep. These findings will be submitted as a research abstract in December 2010 for presentation at the 2011 SLEEP meeting. Understanding how depression and insomnia differ (or are similar) from wakefulness to NREM sleep in adult civilian samples will provide a comparative background to assess how veterans with and without PTSD differ from these two samples (or are similar to) across physiological states.

4. Ms. Jennifer Alman, a neuroscience and biology major at Washington and Jefferson College, completed a research internship in Dr. Germain's lab between May 2009 and August 2009. Her research project focused on assessing central (brain) arousal during REM sleep in participants enrolled in our study with Posttraumatic Stress Disorder (PTSD), in comparison to archival research subjects with Primary Insomnia (PI), good sleepers (GS), and patients with major depressive disorder. Fast-frequency quantitative EEG (qEEG) activity (sigma: 12-16 Hz; beta: 16-32Hz) during REM sleep is used as a potential indicator of central arousal. Although scans for military veterans with PTSD are not yet available, Ms. Alman is complete the background study aimed at investigating the relationships between relative regional cerebral metabolic rate of glucose (rCMRglc) during REM sleep and beta activity in healthy and clinical samples. Analyses are currently under way. This project directly relates to the present study in identifying the potential neurobiological sources of beta activity (a marker of arousal) during REM sleep in healthy and clinical samples, for future comparisons with data to be collected in the present study. The research abstract summarizing these findings was presented as and Oral Presentation at the SLEEP 2010 meeting, and is provided in the appendix.

2. Mr. Daniel Cohen is now a 3rd year medical student at the University of Pittsburgh who completed a summer research project under Dr. Germain's supervision between May and August 2009. Mr. Cohen's project aimed at comparing beta activity during REM sleep in returning veterans with and without PTSD using quantitative EEG analysis. Data processing is almost complete, and analysis will be undertaken in the coming weeks. It is anticipated that a research abstract summarizing these findings were presented as and Oral Presentation at the SLEEP 2010 meeting. As heightened arousal is a core construct of the models to be tested in the present study, evaluating whether group differences in quantitative EEG measures of central arousal may provide some preliminary findings regarding overall hyperarousal during REM sleep in veterans with PTSD compared to veterans without PTSD. The research abstract summarizing these findings is provided in the appendix.

Post-graduate training

3. Dr. Ryan Herringa, 5th year resident in Psychiatry at Western Psychiatric Institute and Clinic (WPIC) was awarded pilot funds from the American Academy of Child and Adolescent Psychiatry to conduct a study exploring the relationships between functional and structural brain characteristics, trauma load, and sleep parameters in returning veterans with and without PTSD. Data collected in Dr. Germain's present study, in combination with studies collected in other projects, will provide pilot data for Dr. Herringa's developing research project. IRB approval has now been secured, and the project will start imminently. It is anticipated that preliminary results obtained from his project will provide the building block for a future NIMH K-award application.

V. CONCLUSION

Recruitment and research activities and procedures remain ongoing. Recruitment of OEF/OIF veterans with PTSD remains difficult, but encouraging signs are observable in the past period of performance. We will expand recruitment to veterans who are currently taking one SSRIs for the treatment of PTSD or sleep disturbances. Other strategies such as enrolling veterans from other conflicts (but within the same age range), or to civilians with PTSD will be reconsidered at a later time if necessary, and in consort with the program officials. We continue to develop collaborative relationships with local veterans' resources at the University as well as regional resources and points of contact for returning military veterans. We have also undertaken more assertive outreach by going directly to local units, as facilitated by the addition of Mr. Paul to our team.

While preliminary results are not expected at this time, we have initiated complementary work using archival imaging data collected in adults with major depression or insomnia, and healthy, civilian control subjects. These analyses and report writing are ongoing, and findings will provide a comparative background for the anticipated findings in veterans with and without PTSD. This will constitute a unique set of comparisons to identify and determine the neurobiological underpinnings that differ among clinical and health samples.

Anticipated imaging data before and after treatment with prazosin or placebo will also provide novel insights in the possible mechanisms underlying sleep treatment response to inform new detection, prevention, and treatment strategies that address both nighttime and daytime symptoms of PTSD and other stress-related disorders in military personnel.

VI. REFERENCES

None applicable.

VII. APPENDIX

- IRB approval letter
- Recruitment flow chart for total period of performance to date.
- Research Abstracts Presented at the 2010 SLEEP Meeting
- Working Draft of Research Abstract for 2011 SLEEP Meeting

SUPPORTING DATA

None to provide at this time.

List of personnel receiving pay from the research effort:

NAME (role)	% effort	Full Time Equivalent
GERMAIN, ANNE (PI)	20%	1
Mammen, Oommen (Co-I and study physician)	10%	1
Phillips, Mary (Co-I)	5%	1
Boarts, Jessica (Research coordinator)	25%	1
Stocker, Ryan (Research coordinator)	25%	1
Richardson, Robin (Assessor)	10%	.7
Good, Rachel (Research Assistant)	100%	1
Rode, Noelle Marie (Data Manager)	19%	.5
Fletcher, Mary (PET Data Manager)	2.5%	1

Appendix

University of Pittsburgh IRB Renewal Approval Letter

Recruitment Flow Chart

Research Abstracts Presented at the 2010 SLEEP Meeting

Working Draft of Research Abstract for 2011 SLEEP Meeting

University of Pittsburgh **OSIRIS** Anne Germain | My Home | Logoff

Home **Help**

Studies > NOSSTIP2 > Approved details

Activity Details (Approved) Application is approved.

Author:	Melanie Holloway (U of Pgh | Other)	**Activity Date:**	7/9/2010 10:27 AM EDT
For Person:		**Created Date:**	7/9/2010 10:27 AM
Logged For (Study):	NOSSTIP2		

Activity Form Property Changes Documents / Tasks / Notifications

University of Pittsburgh
Institutional Review Board

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15213
(412) 383-1480
(412) 383-1508
(fax)
http://www.irb.pitt.edu

Memorandum

To: Anne Germain, PhD
From: Richard Guido, MD, IRB Chair
Date: 7/9/2010
IRB#: PRO10040206
Subject: Neurobiology of Sleep and Sleep Treatment Response in PTSD: Part II

At its full board meeting on 6/16/2010, the University of Pittsburgh Institutional Review Board, Committee E, reviewed the above referenced research study and approved it pending minor modifications. Your responses to these comments have been reviewed and the research submission, in its currently modified form, adequately addresses the concerns of the IRB and is therefore approved.

Please note the following information:

The IRB has approved the waiver for the requirement to obtain a written informed consent for the telephone screening process.

The IRB has approved the advertisements that were submitted for review as written. As a reminder, any changes to the wording of the approved advertisements would require IRB approval prior to distribution.

This study is supported by the following federal grant application(s): PT073961 Neurobiology of Sleep and Sleep Treatment Response in PTSD

The risk level designation is Greater Than Minimal Risk.

Approval Date: 7/8/2010
Expiration Date: 6/15/2011

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. The IRB Reference Manual (Chapter 3, Section 3.3) describes the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

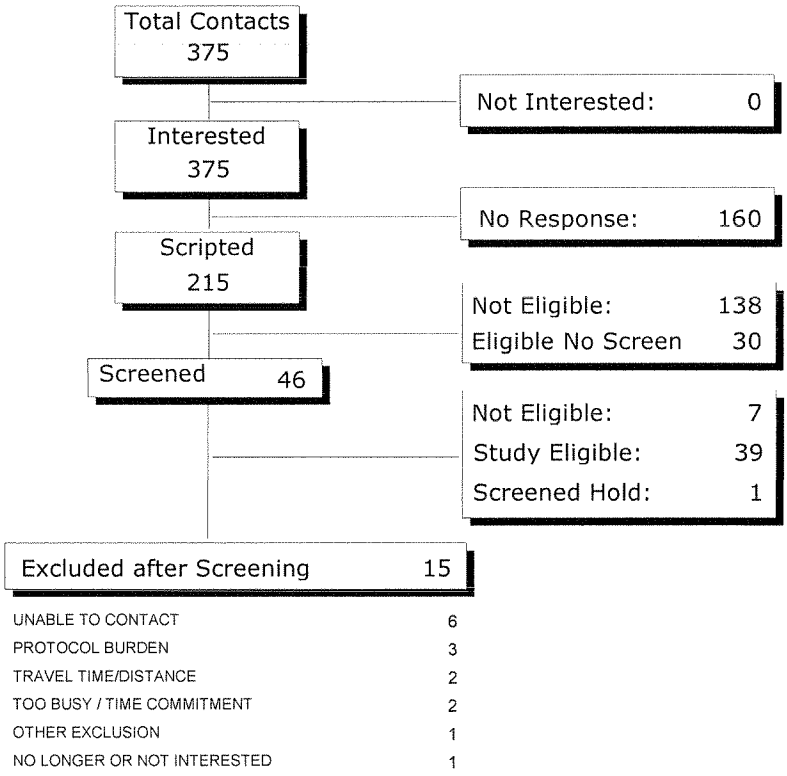
The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of

Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

Participant Flow Report for NOSSTIP

Wednesday, September 08, 2010



CONTROL		PTSD	
Consented	10	Consented	8
Excl/Withdrawn	3	Excl/Withdrawn	5
Baseline Done	**5**	Baseline Done	**0**
Excl/Withdrawn	**0**	Excl/Withdrawn	**0**
Completed Protcol	**5**	Completed Protcol	**0**

CONTROL AGE	CONTROL ID
23	212524
24	214103
24	213019
26	213168
27	213443
28	212945
30	213228
31	212687
33	210858
37	212764

PTSD AGE	PTSD ID
22	213233
26	212950
27	214051
29	213357
31	213002
32	213969
38	214046
42	213166

Abstract:

Title: Quantitative EEG analysis in REM sleep in OEF/OIF combat veterans with and without PTSD.

Authors: Daniel Cohen, Jennie Alman, David Cashmere, Jean Miewald, Anne Germain

Introduction

REM sleep disturbances have been associated with Posttraumatic Stress Disorder (PTSD), but PSG studies have yielded inconsistent findings. In this study, we used quantitative EEG (qEEG) to compare beta activity (16-32Hz) as a measure of central arousal during REM sleep in combat-exposed veterans with and without PTSD. We hypothesized that PTSD would be associated with greater beta activity.

Methods:

Participants were combat veterans of Operations Enduring/Iraqi Freedom (OEF/OIF) drawn from an ongoing clinical trial. Assessments included 2 PSG nights, and questionnaires on sleep quality and psychiatric symptoms. Participants using psychotropic medications were excluded from this analysis. The second PSG night was used for qEEG analysis. Artifacts were rejected in 4-second epochs using an automated algorithm for EMG-twitches, and manually to remove eye-movement and pulse artifacts. Artifact-free REM epochs were subjected to spectral analysis using a fast Fourier transform model. T-tests were used to compare groups. Spearman correlations were performed between beta activity and clinical variables.

Results:
No group differences were observed on PSG measures. The number of 4-second REM epochs rejected for qEEG analysis did not differ between groups. The PTSD group showed lower beta activity in REM sleep than the non-PTSD-group (mean (SD): 0.060 (0.02) vs. 0.096 (0.03), p=0.013). No differences were observed in other qEEG activity bands. In the combined sample, REM beta activity was negatively correlated to PTSD symptom severity (rho=-0.52, p=0.04), PTSD avoidance symptoms (rho=-0.57, p=0.02), but not to hyperarousal symptoms (rho=-0.09, p=0.75).

Discussion:

Contrary to our hypothesis, beta activity was lower during REM sleep in combat veterans with PTSD compared to those without PTSD, and was not related to hyperarousal symptom severity. This small study raises the possibility of a complex, non-linear link between central hyperarousal, REM sleep, and PTSD symptom severity.

Research supported by: This research was supported by the National Institutes of Health (MH053035; MH024652; MH66227; RR024153; R21MH083035-01) and the Department of Defense (PR054093-W81XWH-07-PTSD-IIRA and PT073961-W81XWH-07-PTSD-IIRA).

The Relationship between Absolute Beta Power and rCMRglc in Primary Insomnia during REM Sleep

Jennifer Alman, David Cashmere, Jean Miewald, Eric Nofzinger, M.D., Dan Buysse, M.D., and Anne Germain, Ph.D.

Introduction: Primary (PI) insomnia is characterized by increased arousal and poor sleep. However, the neurobiological correlates of PI during REM sleep have been scarcely studied. We explored the relationship between whole-night absolute beta power during REM sleep and relative regional cerebral metabolic rate of glucose (rCMRglc) in adults with PI.

Methods: 10 PI subjects (M age= 37.86 ± 9.38 years) were included in this analysis. All were medication-free and completed 3 nights of polysomnographic recordings, and [^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography scans during REM sleep. Regression analyses were conducted to evaluate the correlations between whole-night REM sleep absolute power spectral values for beta2 activity (16-32 Hz) and rCMRglc.

Results: No significant positive correlation between beta activity and rCMRglc during REM sleep was observed. Significant negative correlations between beta activity and rCMRglc during REM sleep were observed in three brain areas. The first area (x, y, z coordinates: -10, 48, 10, Z = 3.36, p=0.03) included the left inferior and middle frontal gyri and extended into cingulate gyrus. The largest area (x, y, z coordinates: 52, -66, 14, Z = 4.15, p < .001) encompassed the right inferior, middle, and superior temporal gyri and the fusiform gyrus, parahippocampal gyrus and hippocampus. Bilaterally, it also included the posterior cigulate, precuneus, superior parietal lobule. The last area (x, y, z coordinates: -34, -44, -20, Z = 4.38, p = .04) included the left fusiform gyrus, superior, inferior, and middle temporal gyri.

Conclusion: In adults with PI, decreased whole-night beta activity was associated with increased rCMRglc during REM sleep in bilaterally in temporal and parietal cortices, and in left frontal regions. Posterior brain regions have been related to quiet, resting states. Replication of these preliminary results in large samples is required.

Support:
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Title

Effect of CBT-I on glucose metabolism during NREM sleep and morning wakefulness

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Introduction

Insomnia is a prevalent, debilitating disorder that is thought to arise from psychophysiological arousal. Neuroimaging studies have provided preliminary evidence that the persistence of heightened brain activity from wakefulness to NREM sleep in arousal-regulating regions characterizes adults with insomnia compared to good sleepers.

Here, we investigated whether cognitive-behavioral therapy for insomnia (CBT-I) is associated with reduction in relative regional cerebral metabolic rate of glucose (rCMRglc). We hypothesized that CBT-I would have a discernible effect on glucose metabolism that would reflect dampening of activity in arousal-regulating brain regions.

Methods

Five participants meeting DSM-IV diagnostic criteria for primary insomnia received an 8-week course of CBT-I and completed in-lab sleep and 18-FDG positron emission tomography (PET) studies. After screening and baseline sleep studies, participants completed PET scans during wakefulness and during NREM sleep. Sleep and PET studies were repeated after CBT-I. Statistical analysis of imaging data was performed using SPM8.

Results

Greater post than pre-treatment reduction of relative rCMRglc from morning wakefulness to NREM sleep ($p = 0.011$) was observed in portions of the left temporal and occipital lobes and cerebellum. During both wakefulness and NREM sleep, relative rCMRglc was reduced ($p < 0.05$) in portions of the left and right frontal lobe, thalamus, and right hippocampus, temporal lobe and cerebellum.

Discussion

Consistent with our hypotheses, this pilot study showed that CBT-I is associated with significant reductions in relative rCMRglc during both wakefulness and NREM sleep in the thalamus and frontal cortex. This pattern is consistent with reduction in the thalamocortical network involved in maintenance of arousal. Future directions for investigation include replication in larger samples and comparison of the effects of CBT-I and hypnotic medication on relative rCMRglc.